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Aiming for zero fluid accumulation: First, do no harm

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Abstract

Critically ill patients are often presumed to be in a state of "constant dehydration" or in need of fluid, thereby justifying a continuous infusion with some form of intravenous (IV) fluid, despite their clinical data suggesting otherwise. Overzealous fluid administration and subsequent fluid accumulation and overload are associated with poorer outcomes. Fluids are drugs, and their use should be tailored to meet the patient's individualized needs; fluids should never be given as routine maintenance unless indicated. Before prescribing any fluids, the physician should consider the patient's characteristics and the nature of the illness, and assess the risks and benefits of fluid therapy.

Decisions regarding fluid therapy present a daily challenge in many hospital departments: emergency rooms, regular wards, operating rooms, and intensive care units. Traditional fluid prescription is full of paradigms and unnecessary routines as well as malpractice in the form of choosing the wrong solutions for maintenance or not meeting daily requirements. Prescribing maintenance fluids for patients on oral intake will lead to fluid creep and fluid overload. Fluid overload, defined as a 10% increase in cumulative fluid balance from baseline weight, is an independent predictor for morbidity and mortality, and thus hospital cost. In the last decade, increasing evidence has emerged supporting a restrictive fluid approach.

In this manuscript, we aim to provide a pragmatic description of novel concepts related to the use of IV fluids in critically ill patients, with emphasis on the different indications and common clinical scenarios. We also discuss active deresuscitation, or the timely cessation of fluid administration, with the intention of achieving a zero cumulative fluid balance.

Key words: fluid therapy, oedema, fluid overload, solution, infusion, maintenance, resuscitation, de-escalation, deresuscitation.

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The practice of administering intravenous (IV) fluids originated from the cholera pandemic in 1831, when doctors realized the impact of intravascular volume and electrolyte depletion in significantly dehydrated patients suffering from severe diarrhea [1].

Robert Lewis initiated the first IV infusion in a cholera patient whose condition improved as a result; however, it was not until the 19th century that IV saline management in cholera patients was widely accepted by the medical community. It was only during the 20th century, with the onset of the First World War, that its ability to save lives was tested [1].

Medicine has traditionally focused on therapies based on improving cardiac output. However, it has

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TABLE 1. Impact of fluid overload on the prognosis of critically ill patients

Clinical trial	Year	Intervention	Methodology	Results
FEAST [66]	2013	Group 1: bolus 20 mL kg^{-1} saline 0.9% OR bolus 20 mL kg^{-1} albumin 5% OR maintenance fluids Group 2: bolus 40 mL kg^{-1} normal saline 0.9% OR bolus 40 mL kg^{-1} albumin 5%	Group 1: 3141 paediatric patients with no severe shock Group 2: 29 paediatric patients with severe shock	Mortality at 48 hours Increased mortality in the fluid bolus group RR = 1.45; CI 95%: 1.13–1.86; $P = 0.003$
Positive fluid balance in sepsis [67]	2015	To study whether a positive fluid balance is an independent prognostic factor in patients with sepsis	*n*: 173 37 ICU's	Positive fluid balance was an independent mortality predictor RR = 1.014 (1,007–1,022) per mL kg^{-1}; $P < 0.001$
Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome Meta-analysis [68]	2016	Compared conservative resuscitation to a liberal strategy in patient with sepsis and ARDS	11 units with 2051 patients: adults and children	Neutral mortality Conservative strategy: increased days without MV and reduced length of stay in the ICU
DoReMi [69]	2016	Investigated the impact of daily fluid balance and fluid build-up on mortality in critically ill patients	1734 patients from 21 ICUs from 9 countries	Mortality of 22.3% in patients with acute renal injury and 5.6% in those without acute renal injury ($P < 0.0001$)
CLASSIC [70]	2016	Restrictive fluid management vs. liberal	152 adults with septic shock at ICU	Decreased mortality and decreased acute kidney injury
Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database [71]	2017	To identify the optimal fluid resuscitation strategy in the early hours of severe sepsis and septic shock, whether conservative or aggressive	23,513 patients with severe sepsis and septic shock	In patients receiving volume resuscitation (5 to 9 L), mortality increased by 2.3% (95% CI: 2.0–2.5; $P = 0.0003$) for each additional litre above 5 L
ANDREWS [72]	2017	Early intravenous fluid therapy	112 adults with septic shock in the ER	Increased hospital mortality was observed
Early resuscitation protocol on hospital mortality in adults with sepsis and hypotension: a randomized clinical trial [73]	2017	Early resuscitation for sepsis MAP and Hb goals during resuscitation: MAP > 65 mm Hg, Hb > 7 g dL^{-1}	Randomized clinical trial of 212 adults with sepsis and hypotension	Early resuscitation with intravenous fluids and vasopressors increased hospital mortality compared to regular care
FEDORA [74]	2018	Group 1: Guided via optimised stroke volume, mean blood pressure > 70 mm Hg, and cardiac index ≥ 2.5 L min^{-1} m^{-2} Group 2: Liberal therapy	420 patients in total, 224 patients with guided therapy undergoing elective surgery	Neutral mortality Decreased complications in guided therapy (8.6% vs. 16.6%, $P = 0.018$) Decrease in hospital stay
SWIPE [75]	2018	Resuscitation fluid requirements and physiological responses with albumin 20% vs. albumin 4–5%	Controlled study in 321 adult patients requiring resuscitation with liquids in the first 48 hrs of ICU admission	Resuscitation with albumin 20% decreased resuscitation fluid requirements, decreased positive water balance, not associated with any evidence of damage compared to albumin 4–5%
RELIEF [76]	2018	Liberal vs. restrictive fluid management	3000 adults post surgical abdominal major surgery; randomisation of 1490 patients to fluid restriction and 1493 patients to a liberal fluid strategy	A restrictive fluid regimen was not associated with a higher survival rate but was associated with a higher rate of acute kidney injury
Water overload index in children with sepsis and septic shock [77]	2019	Ratio of water overload and mortality in children with septic shock	Study in 263 children admitted with septic shock at pediatric ICU	Increased morbidity associated with water overload index > 10% (respiratory dysfunction, vasopressor requirement, and renal replacement therapy, as well as higher mortality)
FRESH [78]	2020	Evaluated the responsiveness to liquids as a result of passive leg lift	13 hospitals included 124 patients with sepsis and septic shock Group 1: 83 patients systolic-guided resuscitation Group 2: 41 patients conventionally reanimated	Decreased need for kidney replacement therapy (5.1% vs. 17.5%, $P = 0.04$) Decreased days of mechanical ventilation (17.7% vs. 34.1%, $P = 0.04$) in group 1 compared to the usual attention

ARDS – acute respiratory distress syndrome, ICU – intensive care unit, MV – mechanical ventilation, Hb – haemoglobin, ER – emergency room, MAP – mean arterial pressure

TABLE 2. Complications of fluid overload

Central nervous system	Cerebral oedema ↑ Altered consciousness, stupor, coma Impaired cognition Delirium Intracranial hypertension (ICP ↑) Intracranial compartment syndrome Decreased cerebral perfusion pressure (CPP ↓ = MAP – ICP) Increased intraocular and intra-orbital pressure (IOP ↑) Intra-orbital compartment syndrome
Cardiovascular system	Myocardial oedema ↑ Conduction disturbance Impairment in cardiac contractility Diastolic dysfunction Increased central venous pressure (CVP ↑ and PAOP ↑) Decreased venous return Decreased stroke volume and cardiac output Decrease in (global) ejection fraction Cardio abdominal renal syndrome (CARS) Myocardial depression Pericardial effusion ↑ Increased global end diastolic volume (GEDVI ↑) Increased right ventricular end diastolic volume (RVEDVI ↑)
Respiratory system	Diffusion abnormalities Pulmonary oedema ↑ Pleural effusion ↑ Altered pulmonary and chest wall elastance (cfr IAP ↑) PaO_2 ↓ $PaCO_2$ ↑ PaO_2/FiO_2 ↓ Extra vascular lung water (EVLWI) ↑ Pulmonary vascular permeability index ↑ Lung volumes ↓ (cfr IAP ↑) Prolonged ventilation ↑ Difficult weaning ↑ Work of breathing ↑
Gastrointestinal system	Ascites formation ↑ Gut oedema ↑ Malabsorption ↑ Ileus ↑ Bowel contractility ↓ IAP ↑ and APP (= MAP – IAP) ↓ Abdominal compartment syndrome Success enteral feeding ↓ Intestinal permeability ↑ Bacterial translocation ↑ Splanchnic microcirculatory flow ↓ Decreased indocyanine green plasma disappearance rate (ICG-PDR ↓) Decreased gastric intramucosal pH (pHi ↓)
Hepatic system	Hepatic congestion ↑ Impaired synthetic function Cholestasis ↑ Cytochrome P450 activity ↓ Hepatic compartment syndrome Lactate clearance ↓
Renal system	Renal interstitial oedema ↑ Renal venous pressure ↑ Renal blood flow ↓ Renal interstitial pressure ↑ Renal resistive index ↑ Salt + water retention ↑ Creatinine + uraemia ↑ Glomerular filtration rate (GFR) ↓ Renal vascular resistance ↑ Renal compartment syndrome
Peripheral	Tissue oedema ↑ Poor wound healing ↑ Wound infection ↑ Pressure ulcers ↑ Abdominal wall compliance ↓
Metabolic	Endocrine disturbances Renin angiotensin aldosterone disturbance Altered glucose metabolism CIRCI

CARS – cardio-abdominal renal syndrome, CIRCI – critical illness-related corticosteroid insufficiency, CPP – cerebral perfusion pressure, CVP – central venous pressure, EVLWI – extravascular lung water index, GEDVI – global end diastolic volume index, GFR – glomerular filtration rate, IAP – intra-abdominal pressure, ICG-PDR – indocyanine green plasma disappearance rate, ICP – intracranial pressure, IOP – intra-ocular pressure, MAP – mean arterial pressure, $PaCO_2$ – partial pressure of carbon dioxide, PaO_2 – partial pressure of oxygen, PaO_2/FiO_2 – oxygen arterial pressure/inspired fraction of oxygen, PAOP – pulmonary artery occlusion pressure, pHi – power of hydrogen, RVEDVI – right ventricular end diastolic volume.

been shown in the last decade (Table 1) that this has had no impact on survival; the proposal to improve microcirculatory blood flow without unnecessary IV fluid therapy will ultimately avoid complications associated with medical malpractice (Table 2).

IV fluids are usually an essential component in the management of critically ill hospitalized patients; however, excess fluid administration can cause harm, with an association between fluid accumulation, fluid overload (10% increase), and mortality [2–4].

As Paracelsus stated, "Nothing is without poison; it is the dose that makes the poison." Starting in 2001, Emmanuel Rivers proposed the early application of IV fluids in patients with sepsis and septic shock, setting resuscitation targets with goals to be reached within the first 6 hours. The idea was to achieve adequate oxygen delivery (DO_2) by modifying the determinants of cardiac output and haemoglobin saturation covering the patient's demand, in order to improve microvascular perfusion. At that time, the potential damage caused by excessive fluid administration was yet to be examined [5].

In 2006, the SOAP study showed that fluid over-resuscitation is associated with increased mortality in sepsis patients [2]. Subsequently, the VASST study concluded with similar results, reporting that a positive fluid balance is an independent predictor for mortality [6]. Retrospective analyses of Micek and Sedaka reinforced the potentially harmful effects of over-resuscitation [4].

Despite these findings, it sometimes feels counter-intuitive to manage a hospitalized patient without a baseline IV solution running. While excessive fluid administration is now recognized to have harmful consequences, the administration of IV fluids even within an apparently safe therapeutic range has also been found to have "a dark side" [7]. Current evidence suggests that the risks of overzealous administration of resuscitation or maintenance fluids without a clear indication are outweighed by the benefits. Fluid toxicity depends on the administered dose and composition of the fluid, the natural history of the disease, as well as the patient's susceptibility [2].

The ADQI XII (acute dialysis quality initiating XII) research group proposed a conceptual framework for managing intravenous fluids based on risks related to any drug in order to raise awareness of the potential complications and recognizing the different phases of fluid therapy [8, 9]. Malbrain *et al*. [3] showed in a systematic review that restrictive fluid therapy decreases mortality and the time spent in the intensive care unit (ICU), regardless of the type of solution [2]. They suggested a similar framework illustrating the 4 dynamic phases of fluid therapy and the ROSE acronym (Resuscitation; Optimization; Stabilization; Evacuation) [3].

Analogously to antibiotic therapy, it is time for enhanced fluid stewardship [8, 10].

THE RATIONALE FOR INTRAVENOUS FLUID THERAPY

The NICE (National Institute for Health and Care Excellence) guidelines state that fluid therapy should be administered to patients whose daily fluid needs cannot be reached orally or enterally, and it should be discontinued immediately once this becomes possible [8]. IV fluid administration requires constant vigilance for complications associated with fluid overload. Clinical, radiological, and biochemical markers are currently available to assess fluid status and guide IV fluid administration [2, 11, 12].

Before starting IV fluids, the 4 Ds proposed by Malbrain *et al*. should be considered (Table 3) [3, 8]. It is also important to recognize that the ideal fluid does not exist [13, 14].

INDICATIONS FOR INTRAVENOUS FLUID THERAPY

There are only 6 indications for IV fluids:

1) to replace fluids lost via enteral route or insensible losses (replacement solutions),
2) in patients unable to orally meet the daily needs for water, glucose, and electrolytes, maintenance solutions can be administered,
3) hypovolaemic shock (e.g. blood transfusion in the case of bleeding in trauma) [15],
4) to address daily caloric requirements (enteral or parenteral nutrition),
5) noticeable loss of intravascular volume or when there is a high suspicion thereof, e.g. in severe burns injury or gastrointestinal losses (resuscitation solutions),
6) for the administration of drugs (painkillers, antibiotics, etc.), also known as fluid creep (Figure 1).

Correction of dehydration: replacement fluids

Traditionally, IV fluids have been used to treat decreased intravascular volume in patients in whom the oral or enteral route cannot be used. These include gastrointestinal losses such as vomiting and diarrhoea, fever or hyperthermia, polyuria, lack of access to fluids or alterations in the thirst mechanism (e.g. in older adults), and second and third space losses. In these situations, replacement fluids can help to maintain acceptable blood flow, although the cause of hypovolaemia should be treated as a priority.

Clinical indications triggering the use of IV fluids are as follows: signs of dehydration (dry skin, sunken eyes, dry mucous membranes, loss of skin elasticity), hypotension with systolic pressure < 90 to 100 mm Hg, tachycardia with heart rate > 90 to 100 beats per minute, cognitive dysfunction, encephalopathy, mottled skin, delayed capillary filling > 2 s, cold extremities, and tachypnoea with breath rate > 20 breaths per minute [11, 16, 17]. Standard daily fluid needs are 1 mL kg^{-1} hr^{-1}.

TABLE 3. Intravenous fluid therapy considerations

Drug	Select the type of solution to infuse according to the patient's scenario. As with any drug, fluid prescription comes with indications, contra-indications, and adverse effects.
Dose	Amount of solution to infuse according to the need for fluids (haemodynamic parameters for fluid responsiveness) and response to fluid administration.
Duration	The timeframe during which the fluid will be infused (bolus or continuous infusion).
De-escalation	Time to taper or stop IV fluid therapy.

IV – intravenous

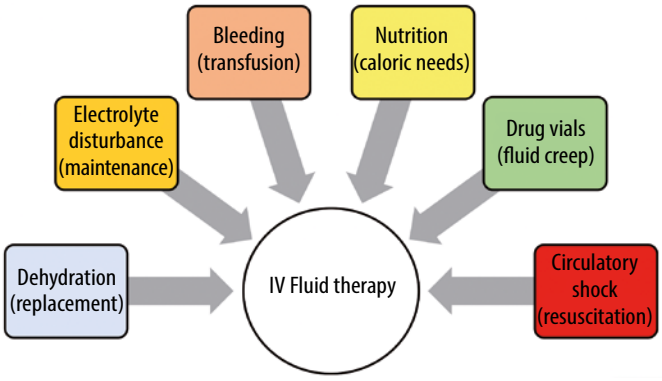

FIGURE 1. Fluid therapy indications

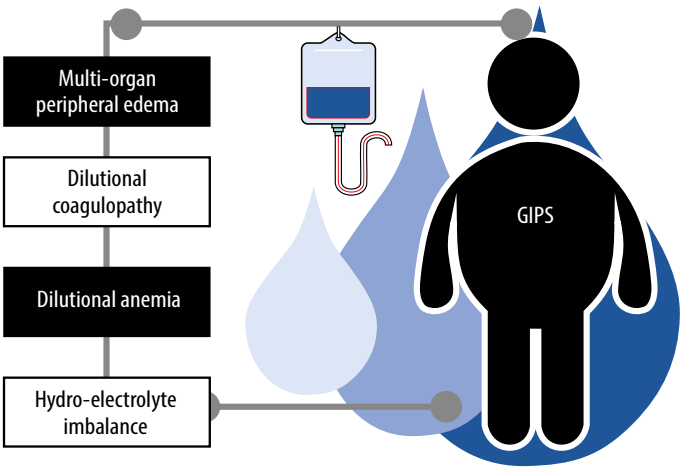

FIGURE 2. Fluid therapy complications. GIPS – global increased permeability syndrome

Electrolyte replacement is an important consideration when prescribing maintenance solutions. Electrolyte disturbances are a common cause for hospital admission and also a common occurrence during hospitalization. Any electrolyte disturbance with clinically significant implications is an indication for IV correction/replacement [18, 19]. The most common electrolyte disturbances (and their respective prevalence) are as follows: hyponatraemia (2.3–44%), hypernatraemia (1.1–4.4%), hypokalaemia (10.2–39%), hyperkalaemia (0.8–13%), hypercalcaemia (0.7–7.5%), hypophosphataemia (0.5–6.5%), hyperphosphataemia (1–17%), and hypomagnesaemia (1.7–8%) [20–24]. The association between hypernatremia levels and mortality is as high as 61% or up to 50% after correction. Another electrolyte disorder associated with poor prognosis is hyperkalaemia, often causes fatal arrhythmias, especially in patients with kidney or cardiovascular disease and diabetes mellitus [25].

Once the diagnosis has been established, the rate of correction should be considered: an infusion at an inappropriate rate may cause complications ranging from local (e.g. potassium IV phlebitis), through chronic systemic (e.g. osmotic sodium demyelination syndrome), to potentially fatal acute systemic complications (cardiac arrhythmias) [19]. The type and volume of fluid in which the electrolyte is to be diluted should also be taken into account, with care to avoid incompatible combinations and excessive volume [19, 25]. Standard daily needs for Na and K are 1.5 and 1 mmol kg^{-1} per day, respectively.

Covering daily fluid requirement: maintenance fluids

During hospitalization one of the most common healthcare activities regarding hydration revolves around measuring fluid balance; the accumulated fluid balance continues to be one of the eponymous numbers on nursing sheets. Simplistically, it equates fluid status with the input and output of fluids in pa-

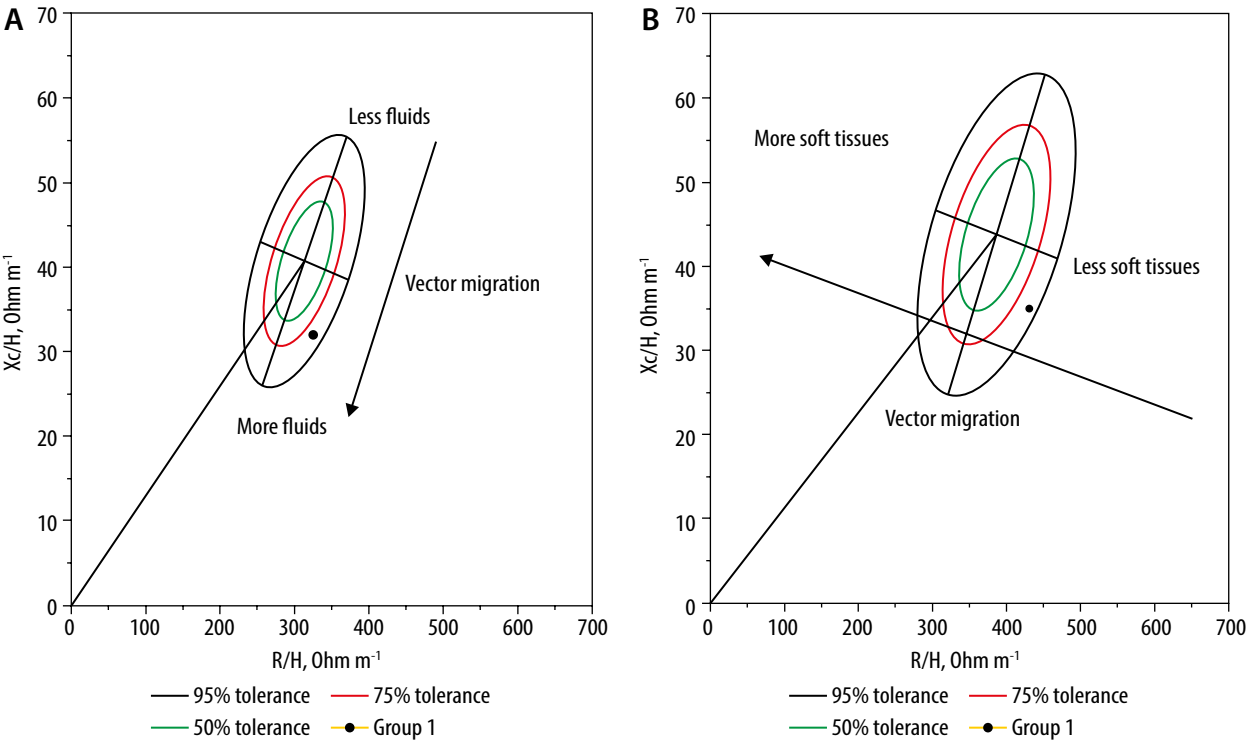

FIGURE 3. RXc graph for male (**A**) and female (**B**), with bioelectrical impedance vector analysis (BIVA). R – resistance (ohms) measured at 50 kHz; Xc – reactance (ohms) measured at 50 kHz; H – height expressed in metres, 50, 75, and 95% tolerance ellipse are shown (green, red, and black ellipse, respectively). Vector migration from less to more body fluids in the male graph and less to more soft tissues in the female graph are shown for schematization
Source: Image courtesy of Eduardo Argaiz performed at National Institute of Medical Sciences and Nutrition Salvador Zubiran

tients. Insensible water loss is challenging to measure, i.e. the amount lost through respiration and skin.

It is acknowledged that accumulated fluid balance figures reported on nursing sheets may not accurately reflect the actual volume state of the patient [26, 27]. A positive or negative balance frequently leads to a presumption that the patient is overhydrated or dehydrated; this paradigm in clinical care will result in misconceptions regarding correct fluid prescription and administration.

The practice of using hypotonic maintenance fluids is based on the Holliday and Segar proposal from 1957 [20, 28] and was recently confirmed in healthy volunteers and critically ill patients [28]. The NICE guidelines recommend an initial prescription of maintenance fluid of 25–30 mL kg^{-1} per day of water [16].

Transfusion of blood products

In haemorrhagic shock, heart rate and arterial vascular tone are increased by compensatory neurohumoral responses in an attempt to maintain sufficient blood flow. However, in the event of severe bleeding, IV fluids maintain sufficient blood flow to the vital organs. Meanwhile, surgical or radiological interventions should be undertaken to stop the bleeding. Prompt recognition of the bleeding will allow initiation of adequate therapy as soon as possible, which can reduce the risk of potentially serious complications (e.g. consumption or dilutional coagulopathy, severe anaemia, cardiac ischaemia, bowel ischaemia, etc.) [29, 30]. The goal of resuscitation is to achieve adequate tissue perfusion and oxygenation while correcting coagulopathy [29]. IV fluids (other than blood) dilute clotting factors, decrease patient temperature, and potentially contribute to acidosis when only chloride-containing solutions (0.9% saline) are used; this will trigger a vicious cycle leading to tissue oedema and organ dysfunction. Eventual alteration of cellular mechanisms causing inflammation result in further complications including cardiac, respiratory, gastrointestinal, and immune dysfunction, hyperfibrinolysis, and increased mortality [15, 17].

Nutrition fluids

Nutrition plays a fundamental role in the management of critically ill patients; recent recommendations support the early introduction of oral, enteral, or intravenous nutrition [31]. Late initiation of nutrition is associated with increased morbidity, gastrointestinal dysfunction, malnutrition, and multiorgan failure. The amount of fluid administered to meet the daily nutritional requirements of a patient ranges between 250 and 500 mL on the first day, to nearly 1.5 L per day in adults, to achieve 25 to 30 kcal kg^{-1} per day. The daily glucose requirements are around 1–1.5 g kg^{-1} per day. Malbrain et al. suggest that the fluids administered through nutritional supplementation should be taken into account within the patient's total fluid balance [8, 32].

Resuscitation fluids

In an unprecedented manner in the history of medicine [33], the initial approach to fluid resuscitation in patients with sepsis had been arbitrarily mandated to consists of "at least 30 mL kg^{-1} of IV crystalloid fluid given within the first 1–3 h" despite a total lack of evidence to support this [34]. This "one size fits all" approach ignores the established literature on the deleterious effects of fluid resuscitation and basic physiology of distributive shock [35]. Many of these recommendations can be traced back to the 2001 Rivers study, which showed that the institution of an Early Goal-Directed Therapy led to decreased mortality amongst septic patients [5].

However, results from previous studies have failed to replicate this benefit [36], with 3 randomized controlled trials demonstrating worse outcomes in patients who received resuscitation with fluid bolus [37–39]. Furthermore, static haemodynamic measurements have been shown to be useless in predicting response from fluid administration, and they have been largely replaced by dynamic indicators of pre-load responsiveness [40]. Using these tools, fluid therapy should be tailored to the patient's physiology rather than indiscriminate infusion of a predefined amount [41].

To avoid fluid overload, 2 complementary approaches may be used: restrictive fluid administration and the active removal of accumulated fluid. The concept of restrictive fluid administration relies on identifying and monitoring signs of fluid responsiveness during ongoing fluid administration, without signs of fluid intolerance. However, it should be emphasized that "fluid responsiveness" in a patient does not always mean that he/she is in need of fluids; giving fluids to a patient until he/she is no longer fluid responsive has not been shown to improve outcomes [40]. The ongoing CLASSIC trial will compare the differences between a liberal vs. restrictive fluid strategy in patients with sepsis. In its pilot feasibility trial, the restrictive fluid strategy led to reduced incidence of acute kidney injury [42].

Active removal of accumulated fluid should be considered simultaneously, given that fluid overload is unlikely to be avoided by conservative fluid strategy alone [8]. After the resuscitation, optimization, and stabilization phases of fluid resuscitation, aggressive fluid removal to achieve a negative fluid balance should be pursued by forced diuresis or ultrafiltration. This strategy has been called Late Goal-

Directed Fluid Removal (LGFR) and should complement a Late Conservative Fluid Management (LCFM) in order to assure a return to euvolaemia [8, 42–46].

Fluid creep

Intravenous delivery of drugs requires fluid to be administered either intermittently or as continuous infusions (e.g. vasopressors, sedatives, etc.). Infused drugs (and the volume in which they are diluted) should be considered as part of the patient's fluid balance.

Some drugs need a large amount of dilutional fluids (e.g. fluconazole, immunoglobulins, etc.). To avoid unnecessary fluid accumulation, drugs administered via continuous infusion should be diluted in the lowest volume possible [20]. A recent study showed that maintenance and replacement fluids accounted for 24.7% of the mean daily total fluid volume, far exceeding resuscitation fluids (6.5%), and were the most important sources of sodium and chloride. Fluid creep represented a striking 32.6% of the mean daily total fluid volume (median 645 mL [IQR 308–1039 mL]) [47].

COMPLICATIONS OF INTRAVENOUS FLUID THERAPY

Overview of secondary impact on end-organ function

"Fluids are not always life-saving"

Liberal IV fluid administration is associated with multi-organ complications secondary to water overload (Table 2) [3]. This is illustrated in Figure 2.

Pulmonary oedema

Normal lung water is about 500 mL in volume (< 7 mL per kg predicted body weight). The lungs need to be dry for normal gas exchange and surfactant function. Pulmonary oedema (increased extravascular lung water) can result from over-resuscitation and is associated with increased morbidity and mortality. Even small increases of approximately 300 mL of excess lung water has a dramatical impact on outcome [43, 48, 49]. In the presence of pulmonary oedema and P/F ratio < 100, fluid therapy needs to be modified to LCFM or LGFR [3]. A common difficulty encountered at the bedside is the early identification of pulmonary oedema [9].

Transpulmonary thermodilution is the current reference standard; a value of extravascular lung water index greater than 10 mL kg^{-1} PBW suggests pulmonary oedema [44]. Pulmonary ultrasound is a simple, non-invasive, and less expensive method. The identification of B-lines correlates with pulmonary oedema when compared to the reference standard [9, 45, 50].

Acute respiratory distress syndrome

Positive fluid balance is associated with deterioration of ventilatory mechanics and worse outcomes in patients with acute respiratory distress syndrome (ARDS) [46]. A meta-analysis published in 2017 assessed the effectiveness of conservative fluid resuscitation strategies compared to a liberal fluid strategy in adults and children with ARDS and sepsis; the conservative treatment group was associated with fewer days on a ventilator and shorter stay in the ICU [51]. Martin *et al*. found that negative fluid balances are associated with improvement in the PaO_2/FiO_2 relationship and haemodynamic parameters [51, 52].

Recently published guidelines recommend a conservative fluid resuscitation approach in ARDS patients, after demonstrating no benefit with liberal fluid management strategies [34, 53].

Interstitial oedema

The main mechanism of oedema formation is the degradation of the endothelial glycocalyx, which is responsible for regulating the permeability and displacement of fluids within the interstitial space. In fluid overload, the lymphatic system loses its ability to drain fluids and promote exchange, so tissue oedema occurs [54, 55]. During critical illness, physical and functional alterations of the glycocalyx lead to a pathological displacement of protein-rich plasma to the interstitium, which can occur even before the water overload affects the haemodynamics [56, 57]. This is referred to as global increased permeability syndrome or GIPS [8, 54] (Figure 2).

Coagulopathy and dilutional anaemia

Excessive administration of IV fluid results in dilution of plasma coagulation factors, alteration of fibrinogen levels [58], and a reduction in the haemoglobin concentration. The loss of capillaries full of erythrocytes, with a reduction in oxygen transport capacity and an ineffective supply of oxygen for the microcirculation, can cause organ dysfunction [59]. The consequent alteration in the haemodynamic state starts a vicious cycle, often resulting in the administration of even more unnecessary fluids [60, 61].

Electrolyte imbalances

Many of the IV solutions in use contain non-physiological concentrations of electrolytes. Unrestricted fluid therapy may lead to an unnecessary disturbance in electrolytes, such as hypo/hypernatraemia, hypo/hyperkalaemia, and hyperchloraemic metabolic acidosis, which, if not identified and treated, can result in organ damage (e.g. kidney injury) [62–64].

Sodium imbalance

A paediatric case-report study by Hoorn reported an association between fluid administration and

hyponatraemia, although this was mainly attributed to the amount of fluid administered (causing a dilutional hyponatraemia) rather than the fluid composition [65]. In situations where renal dilution function is limited (e.g. elevated ADH levels), the infusion of isotonic fluids is associated with hyponatraemia by the desalinization phenomenon; this occurs due to renal excretion of the solutes infused with the rest of the water infused remaining in the intravascular space, thus worsening the hyponatraemia [66].

Potassium imbalance

Studies have demonstrated an increased risk of hyperkalaemia following administration of isotonic fluids compared with balanced solutions (even though balanced solutions contain potassium) – the serum potassium changes may occur via several renal and extrarenal mechanisms related to acidosis; however, no difference in clinical outcomes has been reported [67–69].

Hyperchloraemia

Chloride plays a predominant role in acid-base alteration. Sodium, potassium, chloride, magnesium, and calcium are strong ions that contribute to maintaining a pH of 7.35 to 7.45 under normal conditions [63]. Chloride undergoes free glomerular filtration with 99% reabsorption and excretion of approximately 180 mmol day^{-1}. It is involved in the regulation of the Na–K ATPase pump, inducing the release of renin, vasoconstriction of the renal afferent artery, and reduction of glomerular filtration [70].

A study of healthy volunteers showed that hyperchloraemia is associated with a decreased mean rate of renal artery flow and infusion of renal cortical tissue with consequently decreased urine production [68, 71, 72]. Hyperchloraemic metabolic acidosis can induce vasodilation, decreased cardiac reactivity, decreased release of endogenous catecholamines, increased inflammatory response, and decreased splanchnic perfusion [68, 71, 73].

Infusion of saline solution at 0.9% can induce hyperchloraemia, which is related to metabolic acidosis, and is an independent mortality factor [48, 74].

Abdominal hypertension

Abdominal hypertension (IAH) is defined as a sustained increase in intra-abdominal pressure (IAP) equal to or above 12 mm Hg. A sustained IAP above 20 mm Hg with new-onset organ failure defines abdominal compartment syndrome (ACS) [75]. The major cause of secondary IAH and ACS is fluid overload in the setting of sepsis and capillary leak among other risk factors, e.g. increased intra-abdominal or intraluminal contents and decreased abdominal wall compliance [76–78]. Fluid overload will lead to abdominal wall oedema (with diminished abdominal wall compliance), bowel oedema (leading to ileus), and venous congestion, hence increasing intra-abdominal volume causing a further increase in IAP. Eventually this may lead to increased pressures in other compartments, resulting in cardio-abdominal renal syndrome (CARS) [79, 80] and the polycompartment syndrome [81].

Subgroups with high risk of overhydration

Particular attention should be paid to patients at high risk of overhydration, e.g. those with cardiac, renal, or hepatic failure and nutritional disorders.

Patients with hepatic fibrosis have an increased portal circulation pressure, which can cause plasma leakage at the peritoneal level (ascites). This enhances hypoproteinaemia and in turn aggravates ascites and capillary leakage in a vicious cycle [82].

In patients with advanced chronic kidney disease, decreased filtration leads to fluid accumulation in the second and third space, which can account for up to a 4.5 kg increase in body weight. Correction of fluid accumulation can be achieved with diuretics; therefore, accurate assessment of volaemic status must be performed. A study comparing the effects of normal fluid balance vs. fluid overload in patients on renal replacement therapy for chronic kidney disease demonstrated higher mortality in overhydrated patients [83].

TRIGGERS TO STOP INTRAVENOUS FLUID THERAPY

The traditional approach has been to administer fluids until the patient is no longer fluid responsive. Fluid responsiveness is defined as a 15% increase in cardiac output after fluid resuscitation. However, this strategy may lead to fluid overload [8]. Although fluid overload is associated with increased morbidity and mortality, there are no clear parameters guiding the physician on when to stop fluid administration. Clinical and imaging variables suggesting the presence of interstitial oedema occur late.

Clinical assessment of fluid overload

Clinical parameters of fluid overload are nonspecific and thus not useful to trigger deresuscitation. These include the following: altered mental status, increased hepatojugular reflux, orthopnoea, second and third space fluid accumulation, pitting oedema, altered capillary refill, increased jugular venous pressure, increased body weight, and a positive daily and cumulative fluid balance [11].

Biochemical parameters

Biochemical parameters of fluid overload (haemodilution) are again non-specific. These include the following: increased BNP and pro-NT-BNP, decreased colloid oncotic pressure, signs of infection

and inflammation, increased CRP, decreased albumin and total protein levels, increased serum capillary leakage index (CRP divided by albumin), increased urine albumin over creatinine ratio, presence of AKI (urinalysis), and dilutional anaemia.

Central venous pressure and pulmonary artery occlusion pressure

In 1984 Shippy [84] conducted an analysis of fluid therapy and its relationship to variables such as central venous pressure (CVP), concluding that they do not adequately reflect the volume status of critically ill patients. Therefore, they are not currently recommended for guiding fluid removal [85, 86].

In patients without structural pathology of the right cardiac cavities (e.g. tricuspid disease), CVP reflects right ventricular pressure. This association was initially taken as a strategy to select patients responding to fluid administration based on baseline CVP values and the dynamics of CVP changes after fluid bolus [8]. However, it has been shown that the isolated use of an absolute CVP value does not predict whether a patient will be a fluid responder [35]. At best, CVP can only be considered as a guide to stop IV fluids if it is above normal values (6–8 mm Hg) or if it rises by > 5 mmHg after a fluid bolus (4 mL kg^{-1} 15 min) [62]. The VASST study showed increased mortality associated with fluid overload and high CVP (> 12 mm Hg) [6, 85–87]. A high CVP is also an independent predictor for worsening renal function, not only in patients with decompensated heart failure [88] but also in sepsis [89].

Bioelectrical impedance analysis

Bioelectrical impedance analysis (BIA) is a non-invasive technique used to estimate body composition. It is an inexpensive test [93], with studies demonstrating good correlation with values obtained through the gold standard deuterium dilution method ($r = 0.996$) [94].

The technique has been validated in different patient populations and clinical scenarios for fluid status monitoring [95–97]. Kammar-Garcia *et al*. [98] showed in a prospective observational study of patients admitted to the emergency department that fluid overload as evaluated by bio-electrical impedance vector analysis (BIVA) was significantly related to mortality, and that failure to clinically determine fluid status at time of admission can lead to a mishandling of fluid management in critically ill patients. Fluid overload may already be present at a subclinical level, even before starting IV fluids; BIA evaluation of fluid status at (and during) admission can help guide fluid management [99]. Body weight is often used as a crude measure of fluid balance; however, this does not take into account the skeletal muscle wasting associated with critical illness [100, 101], and therefore cannot provide an accurate reflection. The mortality risk associated with fluid overload (as determined by BIVA) has been documented in hospitalized patients [102] at hospital discharge and at readmission of patients with heart failure, critical illness and those on total renal replacement [103]. Therefore, BIVA, as a non-invasive, low-cost, rapid, and easy technique, could replace accumulated fluid balance as a more accurate and objective parameter of fluid and muscle shift balance (Figure 3).

Imaging techniques

Traditionally, plain chest radiographs were used to assess for signs of fluid overload, including the presence hilar congestion, pleural effusion, Kerley-B lines, etc. However, the subjectiveness of interpretation and static nature of this modality limit its usefulness as a monitoring tool. Critical care ultrasound has superseded plain radiographs as the imaging tool of choice for identification of fluid status. The ease of use, sensitivity for pleural and peritoneal fluid, as well as accessibility for repeated imaging make it ideal for monitoring the dynamic process of fluid resuscitation.

The diameter and variability of the inferior vena cava and internal jugular vein

Measuring the diameter and variability of the inferior vena cava (IVC) and the internal jugular vein (IJV) is another proposed tool for assessing fluid status. A significant change in the diameter of these large vessels during inspiration may be associated with an adequate response to volume; conversely, a variation in the diameter of ICV or IJV < 12% in mechanically ventilated patients or between 36 and 50% in spontaneously breathing patients suggests that no benefit will be gained from further intravenous fluid administration [90, 91].

It has been observed that the normal maximum diameter of the IVC ranges from 1.9 to 2.1 cm; patients presenting with an IVC diameter close to this, with minimal or no variation during the respiratory cycle, do not benefit from IV fluids [44]. The use of the IVC collapsibility index does have some limitations, including inter-observer differences, high rates of false positives, and mild-to-moderate positive predictive value, as discussed in the review paper by Via *et al*. [92]. These include the use of high external PEEP levels, use of non-invasive ventilation, assisted spontaneous breathing (ASB) with low tidal volume, the presence of auto-PEEP, right ventricular dysfunction, tamponade, abdominal hypertension, mechanical obstruction, respiratory variations, or right ventricular myocardial infarction.

TABLE 4. Grading table for assessment of Venous congestion with point-of)-care ultrasound VEXUS = venous congestion assessment with ultrasound (adapted with permission from Rola P. et al book "Bedside Ultrasound: a primer for clinical integration" [129])

Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
IVC	< 5 mm with respiratory variation	5–9 mm with respiratory variation	10–19 mm with respiratory variation	> 20 mm with respiratory variation	20 mm with minimal or no respiratory variation
Hepatic vein	normal S > D	S < D with antegrade S	S flat or inverted or biphasic trace		
Portal vein	< 0.3 pulsatility index	0.3–0.49 pulsatility index	0.5–1.0 pulsatility index		
Renal Doppler	Continuous monophasic/ pulsatile flow	Discontinuous biphasic flow	Discontinuous monophasic flow (diastole only)		
VEXUS score	IVC grade < 3, HV grade 0, PV grade 0 (RV grade 0)	IVC grade 4, but normal HV/PV/RV patterns	IVC grade 4 with mild flow pattern abnormalities in 2 or more of the following HV/PV/RV	IVC grade 4 with severe flow pattern abnormalities in 2 or more of the following HV/PV/RV	

IVC – inferior vena cava, HV – hepatic vein, RV – renal vein, PV – portal vein.

Ultrasonographic evaluation of systemic venous congestion

Pathological elevation of CVP is an important factor for the development of congestive organ damage [88]. In patients with congestive heart failure, the main haemodynamic parameter associated with the development of acute renal injury is the increase in CVP and not the cardiac index (CI) [89]; this is also true in patients with sepsis [104]. Similarly, the severity of congestive liver disease correlates with elevation of right atrial pressure (and hence CVP), not with CI [105].

Organ damage associated with congestion occurs secondarily to the retrograde transmission of CVP to the parenchymatous veins, which alters the venous flow pattern [106]. For example, the transmission of CVP into intra-renal veins generates renosarca and a decrease in renal perfusion pressure (local renal compartment syndrome) [107]. Ultrasound allows direct assessment of blood flow at the organ level using Doppler techniques [108]. Several groups of researchers have found strong associations between organic venous flow disturbances and important outcomes such as acute kidney injury [109], congestive encephalopathy [110], and mortality [111].

The assessment of organ venous congestion should begin by evaluating congestion at the systemic level, i.e. the volume and collapse of the IVC, as previously described. This assessment, performed in the short axis with cephalo-caudal views, provides an impression of the volume of a 3-dimensional structure [112]. An IVC diameter greater than 2 cm with less than 20% collapse on inspiration is considered the first sign of venous congestion [108].

Next, the flow pattern in the portal vein is assessed. Generally, the portal vein is protected from CVP by the resistance generated by the hepatic sinusoids; however, when CVP is pathologically raised, the retrograde pressure can reach the splanchnic pool and affect the venous flow pattern. Therefore, normal portal flow is continuous, but this becomes pulsatile in patients with severe venous congestion. A pulsatile rate greater than 30% is considered moderate congestion, and over 50% is considered severe. Similarly, intra-renal venous flow assessment distinguishes flow patterns associated with congestion. Continuous renal flow is considered normal; this becomes pulsatile, biphasic, and single-phase in order of severity of venous congestion (Table 4) [111].

The combination of these alterations provides not only an estimation of CVP but also an idea of its impact on end organs [108]. In our view, the presence of venous congestion is a powerful argument against the administration of IV fluids, which may exacerbate congestive organ damage regardless of the presence of dynamic volume response predictors. However, there are exceptions (cardiac tamponade, tension pneumothorax, severe chronic pulmonary hypertension), and therefore no decision should be made based on an individual parameter. Of particular importance, in patients with severe venous congestion (portal pulsatility > 50%), the use of diuretics may improve organ function. The diagnosis of venous congestion should not be limited to assessment for its presence and severity; identification and treatment of the underlying cause (e.g. volume overload, congestive heart failure, cardiac tamponade, etc.) are crucial [113].

Figure 4 shows an example of a non-congestive patient and one with severe venous congestion.

The role of venous congestion in the development of worsening organ function in patients with

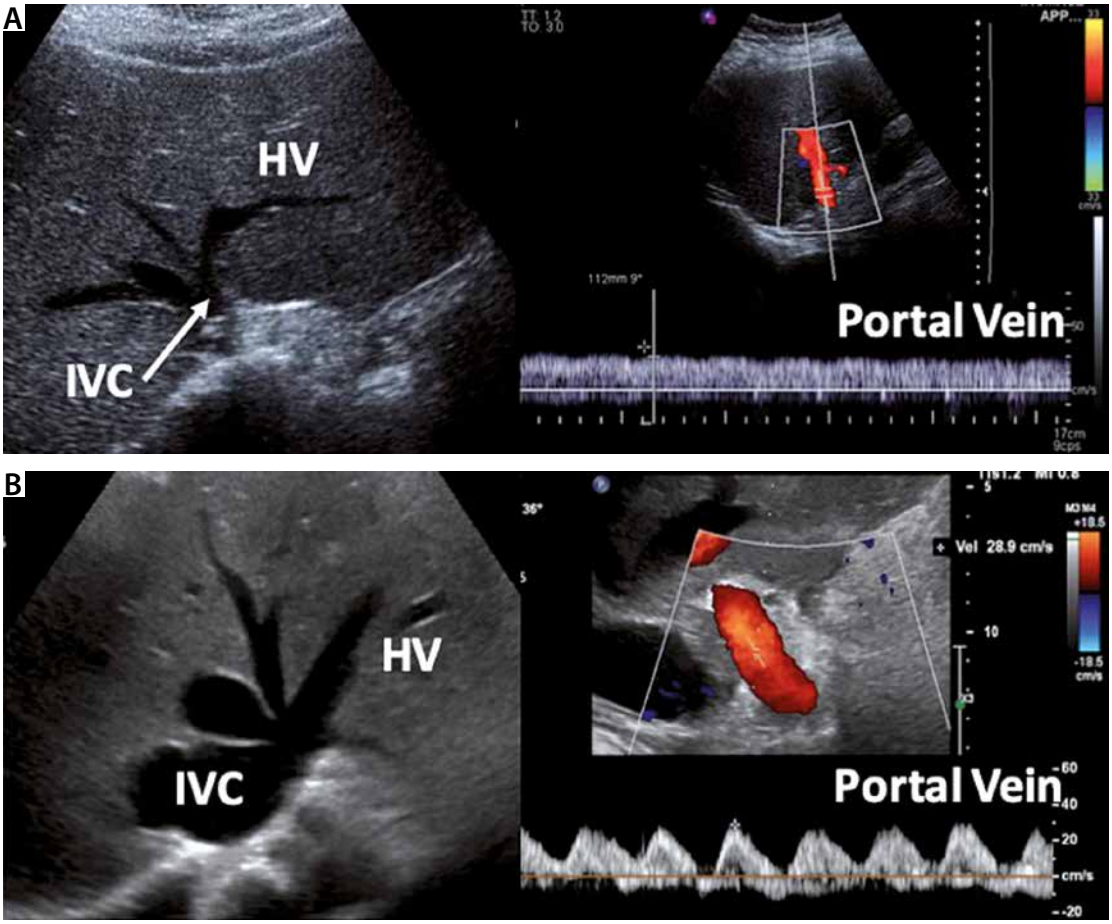

FIGURE 4. **A**) Patient not congestive. Left: Short-axis display of the lower vena cava at the level of the origin of the hepatic veins. IVC diameter: 9 mm. Right: Pulsed Doppler of the portal vein showing minimal pulsatility (continuous flow). **B**) Patient with severe congestion. Left: Short-axis display of the lower vena cava at the level of the origin of the hepatic veins. IVC diameter: 34 mm. Note also the dilation of the supra-hepatic veins. Right: Pulsed Doppler of the portal vein showing 100% pulsatility ($[V_{max} - V_{min}/V_{max}] \times 100$)

fluid overload may explain the improvement in renal function following deresuscitation (either via diuretics or ultrafiltration), as characterized by echocardiographic signs of fluid overload on IVC, portal, hepatic, and renal veins (i.e. sustained distention) (Table 4) [114].

Focused echocardiography

Echocardiography can provide objective data on the patient's volume status and the cardiac response to fluids [61]. A velocity time integral (VTI) > 17 cm infers a normal systolic volume; a change < 12% with fluid administration or passive leg elevation is associated with lack of response to IV fluid administration.

There exist different ultrasound data indicators of right ventricular (RV) failure; these are important because a dysfunctional RV will poorly tolerate preload increases and may paradoxically decrease cardiac output due to ventricular septal interdependence. RV dysfunction is suspected when the RV: LV area increases (RV/LV) > 0.7 to 1 or the tricuspid annular systolic displacement (TAPSE) value is < 8 mm. Caution is needed when interpreting TAPSE in the presence of associated RV failure, chronic pulmonary hypertension, and invasive mechanical ventilation. Left ventricle (LV) function can be evaluated via the ejection fraction (EF), which is the percentage of end-diastolic ejected volume during each heartbeat; an LVEF < 55% suggests inadequate mobilization of blood volume and a tendency for pulmonary and systemic congestion. Different parameters that can help guiding de-escalation of intravenous fluid therapy are listed in Table 5.

FLUID REMOVAL

When a patient does not show fluid-responsiveness on assessment using clinical or dynamic parameters, interventions should be initiated to actively avoid fluid overload, given its possible consequences. Alternative methods are needed to maintain adequate organ perfusion, e.g. early use of vasopressors [113, 115].

As stated above, there are 2 strategies to avoid fluid overload: restriction of IV fluids (prevention) and removal of excess fluid using diuretics or renal replacement therapy with ultrafiltration (intervention) in haemodynamically stable patients [113]. These strategies can be used concurrently.

Achievement of negative fluid balance using deresuscitation strategies within the first 3 days of admission has been associated with decreased mortality compared to that seen in patients who remained in positive fluid balance. Restrictive fluid therapy also resulted in fewer days on mechanical ventilation [43].

In a meta-analysis, Chen *et al*. demonstrated the association of an early furosemide stress test with a loop-diuretic (furosemide)-identified tubular reserve. A positive response in an AKI II subgroup was associated with decreased requirement for renal support and overall mortality rate [116].

Current evidence shows that the greatest sources of fluid accumulation are maintenance solutions (to cover basic daily needs) and fluid creep. This suggests that positive fluid balance is a variable driven by practice, and that it is therefore modifiable [51].

This is especially the case in patients with sepsis (and capillary leak) where higher extravascular lung water values have been reported even without the presence of overt ARDS, suggesting subclinical acute lung injury; and with beneficial effects after deresuscitation strategies [117]. Fluid accumulation in the early course should be avoided in patients with sepsis and ARDS. A multivariate model showed that a more positive fluid balance on the third day was associated with longer durations of ICU admission and mechanical ventilation in survivors, while early fluid removal at this point was associated with better outcomes [40]. Furthermore, in a retrospective matched case-control study of 114 patients on mechanical ventilation with acute pulmonary injury, Cordemans *et al*. found that the application of the multimodal fluid restriction strategy had beneficial effects. The so-called PAL-treatment is an approach that combines high levels of positive end-expiratory pressure (matched to IAP) and small-volume resuscitation with hyperoncotic albumin 20%, followed by fluid removal with furosemide (Lasix®) or ultrafiltration. This approach was associated with negative fluid balance, lower intra-abdominal pressure, lower extravascular lung water index, fewer days of mechanical ventilation and ICU admission, as well as lower 28 day-mortality [43].

THE PARADIGM SHIFT

A paradigm shift in fluid management is occurring; recognition of increased morbidity and mortality related to fluid overload has led modern strategies to place more emphasis on the risks rather than benefits of IV fluid administration.

In healthy individuals, only 25% of a crystalloid bolus remains intravascular after 3 hours; 75% is leaked into the interstitial space. Experimental models of sepsis demonstrate almost complete loss of IV fluids to the interstitium, resulting in pleural effusion, ascites, organ oedema, and impeding organ function. During critical illness, the cytokine storm

TABLE 5. Variables that suggest stopping intravenous fluid therapy

Clinical	
Systolic arterial pressure	> 90 mm Hg
Mean arterial pressure	> 65 mm Hg
Shock index (= HR/SBP)	< 0.5–0.7
Modified shock index	< 0.7–1.3
HR	< 90 a 110 bpm
Peripheral oedema	Godet's sign > 1+
Capillary refill time	< 2.5 s
Diuresis	> 0.5 mL kg^{-1} h^{-1} or >50 mL h^{-1}
No obvious loss of volume or cause of shock resolved	
Biochemistry	
NT-proBNP (pg mL^{-1})	> 450 (< 50 years), > 900 (50 to 75 years), > 1800 (> 75 years)
BNP (pg mL^{-1})	> 500
$ScvO_2$	> 70%
SvO_2	> 65%
Lactate	< 1–2 mmoL L^{-1}
Hb	> 7 g dL^{-1}
Ultrasonography	
Pulmonary ultrasonography	3 or more B-lines in some windows
Portal vein pulsatility	< 30%
Echocardiography	
VTI	> 16 cm
ΔVTI	> 12%
RV/LV relationship	> 0.7
TAPSE	< 18–20 mm
Left ventricular systolic function (visual EF)	< 55%
Haemodynamic	
PPV	< 10–15%
SVV	< 10–15%
PVI	< 14%
CVP	> 6 mm Hg
ΔCVP	> 3 mm Hg post resuscitation
Passive leg raise	< 10% SV increase < 2 mm Hg or 5% increase in $ETCO_2$ < 25% decrease in capillary refill time
Plethysmographic waveform*	

*A small amplitude of the systolic waveform is associated with a decreased systolic volume; conversely, a large amplitude correlates with vasodilation and obviates the need of fluid resuscitation.

HR – heart rate, NT-proBNP – N-terminal pro–B-type natriuretic peptide, $ScvO_2$ – central venous of carbon dioxide saturation, SvO_2 – mixed venous oxygen saturation, VTI – velocity time integral, ΔVTI – delta velocity time integral, RV/LF – right ventricular/left ventricular, TAPSE – tricuspid annular plane systolic excursion, EF – ejection fraction, PPV – pulse pressure variation, SVV – stroke volume variation, PVI – Pleth variability index, CVP – central venous pressure, ΔCVP – delta central venous pressure.

and ensuing capillary leak results in the passage of intravascular free water, electrolytes, proteins, and albumin into the interstitium. It therefore follows that, except where specifically indicated, indiscriminate and aggressive IV fluid administration in critically ill patients is often unnecessary and may be harmful.

The magnitude of positive fluid balance may be considered a biomarker of critical illness. Patients successfully resuscitated from shock usually achieve pro- and anti-inflammatory mediator homeostasis within 3 days; subsequent haemodynamic stabilisation and restoration of plasma oncotic pressure allows diuresis and mobilisation of extravascular fluid to achieve a negative fluid balance. The return of cytokine homeostasis allows repair of the microcirculation and cessation of capillary leak.

In contrast, patients with a persistent systemic inflammatory response fail to reduce transcapillary albumin leakage and accumulate increasingly positive net fluid balances - a state known as Global Increased Permeability Syndrome (GIPS) [54, 55]. Administration of IV fluids in patients with GIPS further increases the pressure in the 4 main compartments of the body: the head, chest, abdomen, and limbs, with the decreased flow gradients in distal organs compromising organ function. Not only should these patients not be given IV fluids, but active steps should also be taken to eliminate excess fluids (LGFR). The ROSE acronym neatly summarizes the dynamic phases of fluid therapy: Resuscitation, Optimization, Stabilization, and Evacuation [3] (Table 6).

Fluid removal can be attempted via loop-diuretics, or a diuretic combination therapy, or even slow continuous ultrafiltration (SCUF), with the aim to restore homeostasis while avoiding deleterious effects such as electrolyte imbalances, metabolic alkalosis and acute renal injury. Comorbidities should also be considered as conditions such as renal or heart

TABLE 6. ROSE diagram illustrating the dynamic phases during fluid therapy (adapted from Malbrain *et al*. with permission [3])

	R (Resuscitation)	O (Optimization)	S (Stabilization)	E (Evacuation)	
Hit	First	Second	Second	Third	Fourth
Cause	Inflammatory response (burn, sepsis, trauma, etc.)	ischemia reperfusion	ischemia reperfusion	Global Increased Permeability Syndrome (GIPS)	Hypoperfusion
Phase	Ebb	Flow	Flow/no Flow	No Flow	No Flow
Type	Severe shock	Unstable	Stable	Recovering	Unstable
Example	Septic shock, burn, multiple trauma, haemorrhagic shock	Less severe burns, diabetic ketoacidosis, gastrointestinal losses	Post-surgical patients with TPN or EN, Replacement of losses in mild pancreatitis	Patients with complete enteral nutrition in critical disease recovery phase, polyuric phase of renal failure	Patients with cirrhosis, anasarca and oedema, GIPS, hepatosplenic hypoperfusion
Question	When to start IV fluids?	When to stop IV fluids?	When to stop IV fluids?	When to start fluid removal?	When to stop fluid removal?
Alternative question	Benefit of IV fluids	Risk of IV fluids	Risk of IV fluids	Benefit of fluid removal	Risk of fluid removal
O_2 transport	Convective alterations	Euvolaemia, normal diffusion	Diffusion alterations	Euvolaemia, normal diffusion	Convective disturbances
Fluids	Mandatory	Critical illness biomarker	Critical illness biomarker	Toxic	–
Fluid therapy	Quick bolus (4 mL kg^{-1} in 10–15 minutes)	Assess fluid balance, use bolus conservatively	Minimal maintenance if oral intake is inadequate, provide replacement fluids	Oral intake if necessary, avoid unnecessary intravenous fluids	Avoid hypoperfusion
Fluid balance	Positive	Neutral	Neutral/Negative	Negative	Neutral
Result	Life saved (rescue)	Organs saved (maintenance)	Organ support (Homeostasis)	Organ recovery (removal)	Organ support
Goals	Macro haemodynamics	Organ perfusion	Organ function	Organ function evolution	Avoid organ hypoperfusion
Objectives	Correct the shock status	Maintain tissue perfusion	Maintain neutral to negative fluid balance	Eliminate fluid build-up	Maintain tissue perfusion
Time to act	Minutes	Hours	Days	Days to weeks	Weeks

GIPS – global increased permeability syndrome, TPN – total parenteral nutrition, EN – enteral nutrition.

disease may limit the response to deresuscitation; development of dynamic prediction models based on daily measures of fluid responsiveness can help identify patients benefiting from diuretics and/or SCUF. The use of hypertonic solutions in combination with diuretics only makes physiological sense in patients with congestive heart failure, whereas in other critically ill patients with normal cardiac function this may have more adverse effects [118].

CONCLUSIONS

Excessive intravenous fluid administration is associated with increased morbidity and mortality. IV fluids should be considered as drugs and only administered where specifically indicated. Critically ill patients will benefit from precise fluid management strategies individualised for their condition – it is not a 'one size fits all' situation, and patients should not be uniformly fluid-resuscitated to the point at which they are no longer fluid-responsive.

Several techniques are available to assess fluid status and monitor progress, with bedside ultrasound showing a great deal of promise as an inexpensive, non-invasive, and accessible tool. Fluid balance is a dynamic process and should be actively managed as such. It is important to identify the patients who will benefit from fluid resuscitation as well as those who should be de-resuscitated.

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REFERENCES

1. Cosnett JE. The origins of intravenous fluid therapy. Lancet 1989; 1: 768-771. doi: 10.1016/s0140-6736(89)92583-x.
2. Pérez-Calatayud ÁA, Díaz-Carrillo MA, Anica-Malagon ED, Briones-Garduño JC. New concepts in intravenous fluid therapy. Cir Cir 2018; 86: 359-365 [Article in Spanish]. doi: 10.24875/CIRU.M18000055.
3. Malbrain MLNG, Marik PE, Witters I, et al. Fluid overload, deresuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiol Intensive Ther 2014; 46: 361-380. doi: 10.5603/AIT.2014.0060.
4. Shahn Z, Shapiro NI, Tyler PD, Talmor D, Lehman LH. Fluid-limiting treatment strategies among sepsis patients in the ICU: a retrospective causal analysis. Crit Care 2020; 24: 62. doi: 10.1186/s13054-020-2767-0.
5. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345: 1368-1377. doi: 10.1056/NEJMoa010307.
6. Boyd JH, Forbes J, Nakada T, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med 2011; 39: 259-265. doi: 10.1097/CCM.0b013e3181feeb15.
7. Reuter DA, Chappell D, Perel A. The dark sides of fluid administration in the critically ill patient. Intensive Care Med 2018; 44: 1138-1140. doi: 10.1007/s00134-017-4989-4.
8. Malbrain MLNG, Van Regenmortel N, Saugel B, et al. Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. Ann Intensive Care 2018; 8: 66. doi: 10.1186/s13613-018-0402-x.
9. Malbrain MLNG, De Tavernier B, Haverals S, et al. Executive summary on the use of ultrasound in the critically ill: consensus report from the 3rd Course on Acute Care Ultrasound (CACU). Anaesthesiol Intensive Ther 2017; 49: 393-411. doi: 10.5603/AIT.a2017.0072.
10. Malbrain ML, Mythen M, Rice TW, Wuyts S. It is time for improved fluid stewardship. ICU Management and Practice 2018; 18: 158-162.
11. Van der Mullen J, Wise R, Vermeulen G, Moonen PJ, Malbrain MLNG. Assessment of hypovolaemia in the critically ill. Anaesthesiol Intensive Ther 2018; 50: 141-149. doi: 10.5603/AIT.a2017.0077.
12. Malbrain MLNG, Huygh J, Dabrowski W, De Waele JJ, Staelens A, Wauters J. The use of bio-electrical impedance analysis (BIA) to guide fluid management, resuscitation and deresuscitation in critically ill patients: a bench-to-bedside review. Anaesthesiol Intensive Ther 2014; 46: 381-391. doi: 10.5603/AIT.2014.0061.
13. Van Regenmortel N, Jorens PG, Malbrain MLNG. Fluid management before, during and after elective surgery. Curr Opin Crit Care 2014; 20: 390-395. doi: 10.1097/MCC.0000000000000113.
14. Malbrain MLNG, Jacobs R, Perner A. The search for the holy grail continues: the difficult journey towards the ideal fluid! J Crit Care 2019; 52: 254-257. doi: 10.1016/j.jcrc.2019.04.015.
15. Wise R, Faurie M, Malbrain MLNG, Hodgson E. Strategies for intravenous fluid resuscitation in trauma patients. World J Surg 2017; 41: 1170-1183. doi: 10.1007/s00268-016-3865-7.
16. Scales K. NICE CG 174: intravenous fluid therapy in adults in hospital. Br J Nurs Mark Allen Publ 2014; 23: S6, S8.
17. Finfer S, Myburgh J, Bellomo R. Intravenous fluid therapy in critically ill adults. Nat Rev Nephrol 2018; 14: 541-557. doi: 10.1038/s41581-018-0044-0.
18. Burton R. Clinical Physiology Of Acid Base An. 3rd ed. New York: McGraw Hill Education; 2000.
19. Weiss-Guillet EM, Takala J, Jakob SM. Diagnosis and management of electrolyte emergencies. Best Pract Res Clin Endocrinol Metab 2003; 17: 623-651. doi: 10.1016/s1521-690x(03)00056-3.
20. Giordano M, Ciarambino T, Castellino P, et al. Diseases associated with electrolyte imbalance in the ED: age-related differences. Am J Emerg Med 2016; 34: 1923-1926. doi: 10.1016/j.ajem.2016.05.056.
21. Lindner G, Pfortmüller CA, Leichtle AB, Fiedler GM, Exadaktylos AK. Age-related variety in electrolyte levels and prevalence of dysnatremias and dyskalemias in patients presenting to the emergency department. Gerontology 2014; 60: 420-423. doi: 10.1159/000360134.
22. Lee CT, Yang CC, Lam KK, Kung CT, Tsai CJ, Chen HC. Hypercalcemia in the emergency department. Am J Med Sci 2006; 331: 119-123. doi: 10.1097/00000441-200603000-00002.
23. Terzian C, Frye EB, Piotrowski ZH. Admission hyponatremia in the elderly: factors influencing prognosis. J Gen Intern Med 1994; 9: 89-91. doi: 10.1007/BF02600208.
24. Lindner G, Felber R, Schwarz C, et al. Hypercalcemia in the ED: prevalence, etiology, and outcome. Am J Emerg Med 2013; 31: 657-660. doi: 10.1016/j.ajem.2012.11.010.
25. Kovesdy CP. Updates in hyperkalemia: outcomes and therapeutic strategies. Rev Endocr Metab Disord 2017; 18: 41-47. doi: 10.1007/s11154-016-9384-x.
26. Perren A, Markmann M, Merlani G, Marone C, Merlani P. Fluid balance in critically ill patients. Should we really rely on it? Minerva Anestesiol 2011; 77: 802-811.
27. Eastwood GM. Evaluating the reliability of recorded fluid balance to approximate body weight change in patients undergoing cardiac surgery. Heart Lung 2006; 35: 27-33. doi: 10.1016/j.hrtlng.2005.06.001.
28. Van Regenmortel N, Hendrickx S, Roelant E, et al. 154 compared to 54 mmol per liter of sodium in intravenous maintenance fluid therapy for adult patients undergoing major thoracic surgery (TOPMAST):

a single-center randomized controlled double-blind trial. Intensive Care Med 2019; 45: 1422-1432. doi: 10.1007/s00134-019-05772-1.
29. Félix-Sifuentes DJ. Hypovolemic shock, a new management approach. Rev Mex Anestesiol 2018; 41(S1): 169-174.
30. Marik PE, Weinmann M. Optimizing fluid therapy in shock. Curr Opin Crit Care 2019; 25: 246-251. doi: 10.1097/MCC.0000000000000604.
31. Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, Casaer MP, Deane AM, et al. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med 2017; 43: 380-398.
32. Malbrain MLNG, Langer T, Annane D, et al. Intravenous fluid therapy in the perioperative and critical care setting: Executive summary of the International Fluid Academy (IFA). Ann Intensive Care 2020; 10: 64.
33. Marik PE, Malbrain MLNG. The SEP-1 quality mandate may be harmful: How to drown a patient with 30 mL per kg fluid! Anaesthesiol Intensive Ther 2017; 49: 323-328.
34. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020; 46: 854-887.
35. Vandervelden S, Malbrain MLNG. Initial resuscitation from severe sepsis: one size does not fit all. Anaesthesiol Intensive Ther 2015; 47 Spec No: s44-55. doi: 10.5603/AIT.a2015.0075.
36. Osborn TM. Severe Sepsis and Septic Shock Trials (ProCESS, ARISE, ProMISe): what is optimal resuscitation? Crit Care Clin 2017; 33: 323-344. doi: 10.1016/j.ccc.2016.12.004.
37. Andrews B, Muchemwa L, Kelly P, Lakhi S, Heimburger DC, Bernard GR. Simplified Severe Sepsis Protocol: a randomized controlled trial of modified early goal-directed therapy in Zambia. Crit Care Med 2014; 42: 2315-2324. doi: 10.1097/CCM.0000000000000541.
38. Andrews B, Semler MW, Muchemwa L, Kelly P, Lakhi S, Heimburger DC, et al. Effect of an early resuscitation protocol on in-hospital mortality among adults with sepsis and hypotension: a randomized clinical trial. JAMA 2017; 318: 1233-1240. doi: 10.1001/jama.2017.10913.
39. Maitland K, Kiguli S, Opoka RO, et al.; FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011; 364: 2483-2495. doi: 10.1056/NEJMoa1101549.
40. Silversides JA, Perner A, Malbrain MLNG. Liberal versus restrictive fluid therapy in critically ill patients. Intensive Care Med 2019; 45: 1440-1442. doi: 10.1007/s00134-019-05713-y.
41. Saugel B, Malbrain MLNG, Perel A. Hemodynamic monitoring in the era of evidence-based medicine. Crit Care Lond Engl 2016; 20: 401. doi: 10.1186/s13054-016-1534-8.
42. Meyhoff TS, Hjortrup PB, Møller MH, et al. Conservative vs liberal fluid therapy in septic shock (CLASSIC) trial – protocol and statistical analysis plan. Acta Anaesthesiol Scand 2019; 63: 1262-1271. doi: 10.1111/aas.13434.
43. Cordemans C, De Laet I, Van Regenmortel N, et al. Aiming for a negative fluid balance in patients with acute lung injury and increased intra-abdominal pressure: a pilot study looking at the effects of PAL-treatment. Ann Intensive Care 2012; 2 Suppl 1: S15.
44. Hofkens PJ, Verrijcken A, Merveille K, et al. Common pitfalls and tips and tricks to get the most out of your transpulmonary thermodilution device: results of a survey and state-of-the-art review. Anaesthesiol Intensive Ther 2015; 47: 89-116. doi: 10.5603/AIT.a2014.0068.
45. Lichtenstein D, van Hooland S, Elbers P, Malbrain MLNG. Ten good reasons to practice ultrasound in critical care. Anaesthesiol Intensive Ther 2014; 46: 323-335. doi: 10.5603/AIT.2014.0056.
46. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network; Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006; 354: 2564-2575. doi: 10.1056/NEJMoa062200.
47. Van Regenmortel N, Verbrugghe W, Roelant E, Van den Wyngaert T, Jorens PG. Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population. Intensive Care Med 2018; 44: 409-417. doi: 10.1007/s00134-018-5147-3.
48. Huber W, Höllthaler J, Schuster T, et al. Association between different indexations of extravascular lung water (EVLW) and PaO2/FiO2: a two-center study in 231 patients. PLoS One 2014; 9: e103854. doi: 10.1371/journal.pone.0103854.
49. Cordemans C, De Laet I, Van Regenmortel N, et al. Fluid management in critically ill patients: the role of extravascular lung water, abdominal hypertension, capillary leak, and fluid balance. Ann Intensive Care 2012; 2 (Suppl 1 Diagnosis and management of intra-abdominal hyperten): S1. doi: 10.1186/2110-5820-2-S1-S1.
50. Lichtenstein DA, Malbrain MLNG. Lung ultrasound in the critically ill (LUCI): a translational discipline. Anaesthesiol Intensive Ther 2017; 49: 430-436. doi: 10.5603/AIT.a2017.0063.
51. Silversides JA, Major E, Ferguson AJ, et al. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. Intensive Care Med 2017; 43: 155-170. doi: 10.1007/s00134-016-4573-3.
52. Martin GS, Mangialardi RJ, Wheeler AP, Dupont WD, Morris JA, Bernard GR. Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury. Crit Care Med 2002; 30: 2175-2182. doi: 10.1097/00003246-200210000-00001.
53. Papazian L, Aubron C, Brochard L, et al. Formal guidelines: management of acute respiratory distress syndrome. Ann Intensive Care 2019; 9: 69. doi: 10.1186/s13613-019-0540-9.
54. Duchesne JC, Kaplan LJ, Balogh ZJ, Malbrain MLNG. Role of permissive hypotension, hypertonic resuscitation and the global increased permeability syndrome in patients with severe hemorrhage: adjuncts to damage control resuscitation to prevent intra-abdominal hypertension. Anaesthesiol Intensive Ther 2015; 47: 143-155. doi: 10.5603/AIT.a2014.0052.
55. Malbrain MLNG, Pelosi P, De laet I, Lattuada M, Hedenstierna G. Lymphatic drainage between thorax and abdomen: please take good care of this well-performing machinery. Acta Clin Belg 2007; 62 Suppl 1: 152-161.
56. Martin GS, Kaufman DA, Marik PE, et al. Perioperative Quality Initiative (POQI) consensus statement on fundamental concepts in perioperative fluid management: fluid responsiveness and venous capacitance. Perioper Med (Lond) 2020; 9: 12. doi: 10.1186/s13741-020-00142-8.
57. Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update 2016. Eur J Anaesthesiol 2017; 34: 332-395. doi: 10.1097/EJA.0000000000000630.
58. Perel A. Iatrogenic hemodilution: a possible cause for avoidable blood transfusions? Crit Care 2017; 21: 291. doi: 10.1186/s13054-017-1872-1.
59. Bakker J, Ince C. Monitoring coherence between the macro and microcirculation in septic shock. Curr Opin Crit Care 2020; 26: 267-272. doi: 10.1097/MCC.0000000000000729.
60. Ince C. Hemodynamic coherence and the rationale for monitoring the microcirculation. Crit Care 2015; 19 (Suppl 3): S8. doi: 10.1186/cc14726.
61. Muckart DJJ. A whiter shade of pale: the ongoing challenge of haemorrhagic shock. Anaesthesiol Intensive Ther 2018; 50: 1-6. doi: 10.5603/AIT.a2017.0060.
62. Rosenkranz S, Howard LS, Gomberg-Maitland M, Hoeper MM. Systemic consequences of pulmonary hypertension and right-sided heart failure. Circulation 2020; 141: 678-693. doi: 10.1161/CIRCULATIONAHA.116.022362.
63. Langer T, Santini A, Scotti E, Van Regenmortel N, Malbrain MLNG, Caironi P. Intravenous balanced solutions: from physiology to clinical evidence. Anaesthesiol Intensive Ther 2015; 47 Spec No: s78-88.
64. Van Regenmortel N, Malbrain M, Jorens P. Integration of acid-base and electrolyte disorders. N Engl J Med 2015; 372: 390. doi: 10.1056/NEJMc1414731.
65. Hoorn EJ, Geary D, Robb M, Halperin ML, Bohn D. Acute hyponatremia related to intravenous fluid administration in hospitalized children: an observational study. Pediatrics 2004; 113: 1279-1284. doi: 10.1542/peds.113.5.1279.
66. Diagnosis and Treatment of Hyponatremia: Compilation of the Guidelines | American Society of Nephrology [Internet]. Available from: https://jasn.asnjournals.org/content/28/5/1340 (Accessed: 21.10.2020).
67. O'Malley CMN, Frumento RJ, Hardy MA, et al. A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. Anesth Analg 2005; 100: 1518-1524. doi: 10.1213/01.ANE.0000150939.28904.81.
68. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg 2012; 256: 18-24. doi: 10.1097/SLA.0b013e318256be72.

69. Khajavi MR, Etezadi F, Moharari RS, et al. Effects of normal saline vs. lactated ringer's during renal transplantation. Ren Fail 2008; 30: 535-539. doi: 10.1080/08860220802064770.
70. Pfortmueller CA, Uehlinger D, von Haehling S, Schefold JC. Serum chloride levels in critical illness – the hidden story. Intensive Care Med Exp 2018; 6: 10. doi: 10.1186/s40635-018-0174-5.
71. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. Clin Sci (Lond) 2003; 104: 17-24.
72. Serpa Neto A, Martin Loeches I, Klanderman RB, et al. Balanced versus isotonic saline resuscitation-a systematic review and meta-analysis of randomized controlled trials in operation rooms and intensive care units. Ann Transl Med 2017; 5: 323. doi: 10.21037/atm.2017.07.38.
73. Lee JY, Hong TH, Lee KW, Jung MJ, Lee JG, Lee SH. Hyperchloremia is associated with 30-day mortality in major trauma patients: a retrospective observational study. Scand J Trauma Resusc Emerg Med 2016; 24: 117. doi: 10.1186/s13049-016-0311-7.
74. Sen A, Keener CM, Sileanu FE, et al. Chloride content of fluids used for large-volume resuscitation is associated with reduced survival. Crit Care Med 2017; 45: e146-153. doi: 10.1097/CCM.0000000000002063.
75. Kirkpatrick AW, Roberts DJ, De Waele J, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med 2013; 39: 1190-1206. doi: 10.1007/s00134-013-2906-z.
76. Malbrain MLNG, Peeters Y, Wise R. The neglected role of abdominal compliance in organ-organ interactions. Crit Care Lond Engl 2016; 20: 67. doi: 10.1186/s13054-016-1220-x.
77. Malbrain MLNG, Chiumello D, Cesana BM, et al. A systematic review and individual patient data meta-analysis on intra-abdominal hypertension in critically ill patients: the wake-up project. World initiative on Abdominal Hypertension Epidemiology, a Unifying Project (WAKE-Up!). Minerva Anestesiol 2014; 80: 293-306.
78. Malbrain MLNG, Chiumello D, Pelosi P, et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. Crit Care Med 2005; 33: 315-322. doi: 10.1097/01.ccm.0000153408.09806.1b.
79. Bagshaw SM, Verbrugge FH, Mullens W, Malbrain MLNG, Davenport A. Kidney-organ interaction. In: Oudemans-van Straaten HM, Forni LG, Groeneveld ABJ, et al. (eds.). Acute Nephrology for the Critical Care Physician [Internet]. Cham: Springer International Publishing; 2015 [cited 2020 Jun 3]. p. 69–85. Available from: https://doi.org/10.1007/978-3-319-17389-4_6.
80. Verbrugge FH, Dupont M, Steels P, et al. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. J Am Coll Cardiol 2013; 62: 485-495. doi: 10.1016/j.jacc.2013.04.070.
81. Malbrain MLNG, Roberts DJ, Sugrue M, et al. The polycompartment syndrome: a concise state-of-the-art review. Anaesthesiol Intensive Ther 2014; 46: 433-450. doi: 10.5603/AIT.2014.0064.
82. Nadim MK, Durand F, Kellum JA, et al. Management of the critically ill patient with cirrhosis: a multidisciplinary perspective. J Hepatol 2016; 64: 717-735. doi: 10.1016/j.jhep.2016.05.001.
83. Prencipe M, Granata A, D'Amelio A, Romano G, Aucella F, Fiorini F. Usefulness of US imaging in overhydrated nephropathic patients. J Ultrasound 2016; 19: 7-13. doi: 10.1007/s40477-014-0152-z.
84. Shippy C, Appel P, Shoemaker W. Reliability of clinical monitoring to assess blood volume in critically ill patients. Crit Care Med 1984; 12: 107-112. doi: 10.1097/00003246-198402000-00005.
85. Magder S. More respect for the CVP. Intensive Care Med 1998; 24: 651-653. doi: 10.1007/s001340050640.
86. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest 2008; 134: 172-178. doi: 10.1378/chest.07-2331.
87. Su L, Pan P, Li D, et al. Central venous pressure (CVP) reduction associated with higher cardiac output (CO) favors good prognosis of circulatory shock: a single-center, retrospective cohort study. Front Med 2019; 6: 216. doi: 10.3389/fmed.2019.00216.
88. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009; 53: 589-596. doi: 10.1016/j.jacc.2008.05.068.
89. Legrand M, Dupuis C, Simon C, et al. Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study. Crit Care Lond Engl 2013; 17: R278. doi: 10.1186/cc13133.
90. Muller L, Bobbia X, Toumi M, et al. Respiratory variations of inferior vena cava diameter to predict fluid responsiveness in spontaneously breathing patients with acute circulatory failure: need for a cautious use. Crit Care Lond Engl 2012; 16: R188. doi: 10.1186/cc11672.
91. Dipti A, Soucy Z, Surana A, Chandra S. Role of inferior vena cava diameter in assessment of volume status: a meta-analysis. Am J Emerg Med 2012; 30: 1414-1419.e1. doi: 10.1016/j.ajem.2011.10.017.
92. Via G, Tavazzi G, Price S. Ten situations where inferior vena cava ultrasound may fail to accurately predict fluid responsiveness: a physiologically based point of view. Intensive Care Med 2016; 42: 1164-1167. doi: 10.1007/s00134-016-4357-9.
93. Lukaski HC, Johnson PE, Bolonchuk WW, Lykken GI. Assessment of fat-free mass using bioelectrical impedance measurements of the human body. Am J Clin Nutr 1985; 41: 810-817. doi: 10.1093/ajcn/ 41.4.810.
94. Piccoli A. Whole body – single frequency bioimpedance. Contrib Nephrol 2005; 149: 150-161. doi: 10.1159/000085478.
95. Lyons KJ, Bischoff MK, Fonarow GC, Horwich TB. Noninvasive bioelectrical impedance for predicting clinical outcomes in outpatients with heart failure. Crit Pathw Cardiol 2017; 16: 32-36. doi: 10.1097/HPC.0000000000000105.
96. Abad S, Sotomayor G, Vega A, et al. The phase angle of the electrical impedance is a predictor of long-term survival in dialysis patients. Nefrol Publicacion Of Soc Espanola Nefrol 2011; 31: 670-676. doi: 10.3265/Nefrologia.pre2011.Sep.10999.
97. Rhee H, Jang KS, Shin MJ, et al. Use of multifrequency bioimpedance analysis in male patients with acute kidney injury who are undergoing continuous veno-venous hemodiafiltration. PLoS One 2015; 10: e0133199. doi: 10.1371/journal.pone.0133199.
98. Kammar-García A, Pérez-Morales Z, Castillo-Martinez L, et al. Mortality in adult patients with fluid overload evaluated by BIVA upon admission to the emergency department. Postgrad Med J 2018; 94: 386-391. doi: 10.1136/postgradmedj-2018-135695.
99. Kammar-García A, Castillo-Martínez L, Villanueva-Juárez JL, et al. Comparison of bioelectrical impedance analysis parameters for the detection of fluid overload in the prediction of mortality in patients admitted at the emergency department. JPEN J Parenter Enteral Nutr 2021; 45: 414-422. doi: 10.1002/jpen.1848.
100. Wischmeyer PE, Puthucheary Z, San Millán I, Butz D, Grocott MPW. Muscle mass and physical recovery in ICU: innovations for targeting of nutrition and exercise. Curr Opin Crit Care 2017; 23: 269-278. doi: 10.1097/MCC.0000000000000431.
101. Lee SY, Ahn S, Kim YJ, et al. Comparison between dual-energy x-ray absorptiometry and bioelectrical impedance analyses for accuracy in measuring whole body muscle mass and appendicular skeletal muscle mass. Nutrients 2018; 10: 738. doi: 10.3390/nu10060738.
102. Santarelli S, Russo V, Lalle I, et al. Prognostic value of decreased peripheral congestion detected by Bioelectrical Impedance Vector Analysis (BIVA) in patients hospitalized for acute heart failure: BIVA prognostic value in acute heart failure. Eur Heart J Acute Cardiovasc Care 2017; 6: 339-347. doi: 10.1177/2048872616641281.
103. Basso F, Berdin G, Virzì GM, et al. Fluid management in the intensive care unit: bioelectrical impedance vector analysis as a tool to assess hydration status and optimal fluid balance in critically ill patients. Blood Purif 2013; 36: 192-199. doi: 10.1159/000356366.
104. Dai DF, Swanson PE, Krieger EV, Liou IW, Carithers RL, Yeh MM. Congestive hepatic fibrosis score: a novel histologic assessment of clinical severity. Mod Pathol 2014; 27: 1552-1558. doi: 10.1038/modpathol.2014.79.
105. Tang WHW, Kitai T. Intrarenal venous flow: a window into the congestive kidney failure phenotype of heart failure? JACC Heart Fail 2016; 4: 683-686. doi: 10.1016/j.jchf.2016.05.009.
106. Beaubien-Souligny W, Rola P, Haycock K, et al. Quantifying systemic congestion with Point-Of-Care ultrasound: development of the venous excess ultrasound grading system. Ultrasound J 2020; 12: 16. doi: 10.1186/s13089-020-00163-w.
107. Hise AC da R, Gonzalez MC. Assessment of hydration status using bioelectrical impedance vector analysis in critical patients with acute kidney injury. Clin Nutr Edinb Scotl 2018; 37: 695-700. doi: 10.1016/j.clnu.2017.02.016.
108. Beaubien-Souligny W, Benkreira A, Robillard P, et al. Alterations in portal vein flow and intrarenal venous flow are associated with acute kidney injury after cardiac surgery: a prospective observational cohort study. J Am Heart Assoc 2018; 7: e009961. doi: 10.1161/JAHA.118.009961.
109. Benkreira A, Beaubien-Souligny W, Mailhot T, et al. Portal hypertension is associated with congestive encephalopathy and delirium after cardiac surgery. Can J Cardiol 2019; 35: 1134-1141. doi: 10.1016/j.cjca.2019.04.006.

110. Iida N, Seo Y, Sai S, et al. Clinical implications of intrarenal hemodynamic evaluation by Doppler ultrasonography in heart failure. JACC Heart Fail 2016; 4: 674-682. doi: 10.1016/j.jchf.2016.03.016.
111. Huguet R, Fard D, d'Humieres T, et al. Three-dimensional inferior vena cava for assessing central venous pressure in patients with cardiogenic shock. J Am Soc Echocardiogr 2018; 31: 1034-1043. doi: 10.1016/j.echo.2018.04.003.
112. Greenway CV, Lautt WW. Distensibility of hepatic venous resistance sites and consequences on portal pressure. Am J Physiol-Heart Circ Physiol 1988; 254: H452-458. doi: 10.1152/ajpheart.1988.254.3.H452.
113. Acheampong A, Vincent JL. A positive fluid balance is an independent prognostic factor in patients with sepsis. Crit Care 2015; 19: 251. doi: 10.1186/s13054-015-0970-1.
114. Testani JM, Khera AV, St John Sutton MG, et al. Effect of right ventricular function and venous congestion on cardiorenal interactions during the treatment of decompensated heart failure. Am J Cardiol 2010; 105: 511-516. doi: 10.1016/j.amjcard.2009.10.020.
115. Jacobs R, Lochy S, Malbrain MLNG. Phenylephrine-induced recruitable preload from the venous side. J Clin Monit Comput 2019; 33: 373-376. doi: 10.1007/s10877-018-0225-1.
116. Chen JJ, Chang CH, Huang YT, Kuo G. Furosemide stress test as a predictive marker of acute kidney injury progression or renal replacement therapy: a systemic review and meta-analysis. Crit Care Lond Engl 2020; 24: 202. doi: 10.1186/s13054-020-02912-8.
117. Martin GS, Eaton S, Mealer M, Moss M. Extravascular lung water in patients with severe sepsis: a prospective cohort study. Crit Care Lond Engl 2005; 9: R74-82. doi: 10.1186/cc3025.
118. Lal A, Garces JPD. Physiologic approach to diuresis in de-resuscitation phase in intensive care. Crit Care 2020; 24: 270. doi: 10.1186/s13054-020-02900-y.